

REMARKS

Applicants acknowledge with appreciation the cordial telephone interview held June 21, 2007 between Examiner Crane and their undersigned counsel during which the Examiner indicated that submitted Declaration of the inventors was acceptable. Applicants thank the Examiner for his consideration.

The indication of allowable subject matter in claim 7 is also acknowledged with appreciation.

With regard to the requested cross-reference to related application, attention is directed to the Application Data Sheet submitted October 7, 2005 and the provisions of 37 C.F.R. 1.76(b)(5).

The typographical error noted by the Examiner on page 26 has been corrected by this Amendment, as well as an additional error on page 2. Claims 1-11 also have been rewritten as new claims 12-22 in order to eliminate the informalities noted by the Examiner. Support for the amended claims is found, *inter alia*, in original claims 1-11. Applicants thank the Examiner for bringing these items to their attention.

Any grounds which may have existed for the rejection of claims 4-11 under 35 U.S.C. §112, second paragraph, are believed obviated by the foregoing amendments, and reconsideration and withdrawal of the rejection are respectfully requested.

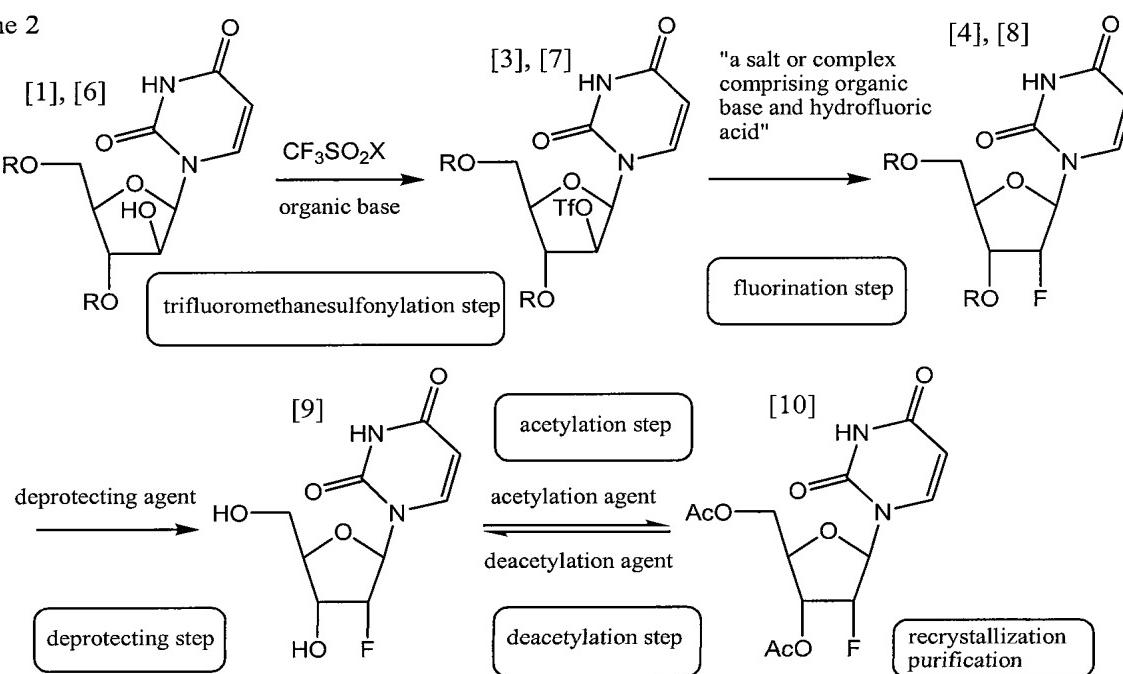
Insofar as the rejection of claims 1-6 and 8-11 under 35 U.S.C. §103(a) over Ikehara et al., *J. Carbohydrates Nucleosides Nucleotides*, 7(2):131-140 (1980) in view of Hayakawa et al., *Chem. Pharm. Bull. (Japan)*, 38(5):1136-39 (1990) may be thought applicable to the amended claims, it is respectfully traversed.

Firstly, the reaction substrate (i.e., 3',5'-hydroxyl-protected, 1- β -D-arabinofuranosyluracil represented by formula [1] or [6]) of the claimed invention according to the amended claims 12-15, 17 and 19-22 is substantially different from the compound of Ikehara et al., which is cited as Non-patent Publication 5 in the specification (page 1, lines 26-28). Furthermore, the claimed

invention of the amended claims 12-15, 17, and 19-22 is different from Ikehara et al. with respect to the first and second points. The first point is that an organic base (e.g., triethylamine) is used as the base in the trifluomethanesulfonylation, as shown in the following scheme 2, which is the same as that of page 12, line 14 of the specification, except that the numbers of [1], [6], [3], [7], [4], [8], [9] and [10] of the formulas were added.

The second point is that a salt or complex containing an organic base and hydrofluoric acid is used as the fluorinating agent in the fluorination step. This salt or complex has a relatively low price. The inventors have unexpectedly found that the yield is remarkably improved by the above-underlined first and second points and by using 3',5'-hydroxyl-protected, 1- β -D-arabinofuranosyluracil represented by formula [1] or [6] as the reaction substrate (see page 8, lines 1-19; and page 9, lines 2-12 of the specification).

Scheme 2



In contrast with the claimed invention according the amended claims 1-4, 6, and 8-11, Ikehara et al. lacks the above-underlined first and second points and has a problem in which "an elimination reaction of a triflate group (CF_3SO_3^-

group)" occurs competitively as a side reaction, and in which a double-bond containing by-product is produced notably (see page 2, lines 12-25 of the specification). Specifically, Ikehara et al. (page 133) uses NaH (an inorganic base) as the base in the trifluoromethanesulfonylation step of the compound III and uses tetra-n-butylammonium fluoride (nBut)₄N⁺F⁻, which is a quaternary ammonium salt, as the fluorinating agent in the fluorination step of the compound IV. Thus, yield of the dehydroxyfluorination or deoxyfluorination (i.e., the two-step reaction from the compound III to the compound V through the compound IV) according to Ikehara et al. was 8%, which is extremely low. This 8% was determined by multiplying 36% (see page 134, line 12 of Ikehara et al.) by 0.21 (see page 134, line 20 of Ikehara et al.).

In contrast with Ikehara et al., the present inventors have unexpectedly and surprisingly found that the presently claimed invention produces the target fluorinated product (i.e., the compound [4] or [9] in the scheme 2) with a yield of 70% or higher (see Examples 1-9 (e.g., page 41, lines 5-8) of the specification) by the above-underlined first and second points in the deoxyfluorination (i.e., the two- or three-step reaction from the compound [1] to the compound [4] or [9]) of the 1-β-D-arabinofuranosyluracil derivative (i.e., the compound [1]). This yield is far superior to that of Ikehara et al. A process for achieving the deoxyfluorination with such a high yield as in the claimed invention is not disclosed nor suggested by Ikehara et al.

In contrast with the claimed invention, Hayakawa et al. discloses a deoxyfluorination by the DAST, which is mentioned on page 1, lines 9-10 and 14-16, and the above-amended paragraph on page 2, lines 8-11 of the specification. Although DAST is a reagent commonly used at a small-scale laboratory level, it is a special fluorination agent that is very expensive and problematic to handle in large amounts. Therefore, DAST is absolutely inappropriate to be used in a deoxyfluorination in industrial scale. Pointedly, the present invention provides a high-yield deoxyfluorination without using a high-price fluorination agent such as DAST.

Furthermore, even by using DAST, only ordinary reaction yields are obtained (see the above-amended paragraph on page 2, lines 8-11 of the specification; and the right column on page 1137 of Hayakawa et al.). In contrast with this, the deoxyfluorination of the claimed invention provides an even higher yield (70% or higher).

As mentioned above, the present invention produces the target fluorination product (the compound [4], [8] or [9]) in unexpectedly and surprisingly high yield, while greatly suppressing the elimination reaction (see page 2, lines 18-21 of the specification), by the above-underlined first and second points in the deoxyfluorination of the 1- β -D-arabinofuranosyluracil derivative (i.e., the compound [1] or [6]). Such a result would not be achieved even if a skilled worker were to attempt to combine the teachings of Ikehara et al. and Hayakawa et al.. Therefore, Applicants respectfully submit that claims 12-15, 17 and 19-22 are non-obvious over the combination of Ikehara et al. and Hayakawa et al.

It should be noted that according to claim 13, 14 and 19-22, a fluorinating agent comprising a salt or complex containing triethylamine and hydrofluoric acid must be used. The use of this fluorinating agent is particularly preferred (see page 8, line 8 to page 9, line 12 of the specification) and is not disclosed nor suggested at all by the cited references. Therefore, claims 13, 14 and 19-22 are submitted to be allowable for this additional reason as well.

Furthermore, according to claim 14, 21 and 22, the hydroxyl-protecting groups of the 2'-triflate compound represented by formula [7] are limited to tetrahydropyranyl groups (THP) (see page 9, line 13 to page 10, line 3 of the specification). Therefore, this claims should be allowable for the same reasons original claim 7 was indicated to contain allowable subject matter.

Moreover, the invention as defined in claim 16 for purifying the final target compound, 2'-deoxy-2'-fluorouridine represented by the formula [9] (see page 2, line 2 to page 3, line 6; and particularly page 11, lines 13-25 of the

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specification), is not disclosed or suggested by the combination of Ikehara et al. and Hayakawa et al . and is likewise allowable.

Thus, Ikehara et al. in combination with Hayakawa et al. fails to make out a proper, *prima facie*, case of obviousness with respect to the presently claimed invention, and reconsideration and withdrawal of the rejection are respectfully requested.

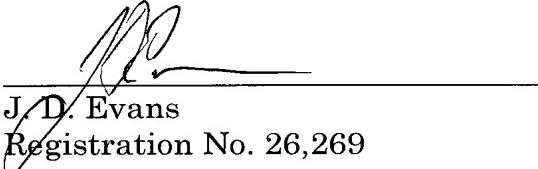
In view of the foregoing amendments and remarks, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned at (202) 624-2845 would be appreciated since this should expedite the examination of the application.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #038788.56805US).

Respectfully submitted,

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